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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,874	10/30/2001	James Alun Wynne Morgan	13384-002001	1385

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,874	MORGAN ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/31/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *53-55, 65* is/are allowed.

6)☒ Claim(s) *56-64 and 66-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 53-70 are pending.

Applicant's traversal, the addition of claims 53-70 and the cancellation of claims 1-52 in paper filed on 1/31/05 is acknowledged and considered.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/31/05 has been entered.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Claim 58 is not present in the claim listing. Accordingly, misnumbered claims 59-70 have been renumbered 58-69. The response to the instant office action should reflect the renumbering of the claims, including proper dependency of dependent claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-64 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation 'the isolated nucleic acid molecule hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in .368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode' in new claim 57 and claims dependent therefrom is not supported by the as-filed specification. Applicant has cited a page (page 16) for where the limitation in the new claim is supposedly supported, however, there does not appear to be a written description of the claim limitation in the application as filed. See MPEP § 2163.06. Page 16 displays a common formula from a Laboratory Manual for calculating stringency conditions of a specified sequence homology. Page 16 further recites:

> The Tm of a DNA duplex increases by 1-1.5°C with every 1% decrease in homology. Thus, targets with greater than about 75% sequence identity would be observed using a hybridization temperature of 42°C. Such a sequence would be considered substantially homologous to the nucleic acid sequence of the present invention.

The specification and the art of record do not provide support for correlating the term "substantially homologous" to a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23. In addition, there is no indication

on page 16 for which nucleic acid sequence of the present invention is being referred to. There are several nucleic acid sequences that are considered a nucleic acid sequence of the present invention, e.g., SEQ ID NO: 52, 13-1f, p14-2f, including a nucleic acid encoding the amino acid sequence set forth in SEQ ID NO: 23. However, nothing in the specification would lead one to the particular limitation as set forth in the new claims.

> "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose."
>
> *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Page 16 provides support for '[Na+] = [0.368] and 50% formamide, with GC content of 42% and an average prove size of 200 bases, the Tm is 57°C' and not the limitation recited in the new claims.

In addition, the additional limitations in new claims 60-64 in combination with the limitation in claim 57 are not supported by the specification. See *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

It is apparent that the applicants at the time the invention was made did not intend or contemplate the limitation recited in the new claim and claims dependent therefrom as part of the disclosure of their invention. There is no evidence in the specification that the applicants were in possession of the claimed nucleotide sequence as set forth in the claims, as it is now claimed, and claims dependent therefrom at the time the application was filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-64 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 57-64 and 66-70, as best understood, are readable on a genus of isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode, wherein the genus of isolated nucleic acid sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of isolated nucleic molecules that encode a polypeptide with at least 70% identity to the polypeptide set forth in SEQ ID NO: 23

and is a nematode control agent. The specification further contemplates methods of producing the polypeptide. The applicants disclosed methods of assessing homology at the nucleic acid level by hybridization screening. More specifically, page 16 recites:

> One common formula for calculating the stringency conditions required to achieve hybridization between two nucleic acid molecules of a specified sequence homology in a Laboratory Manual:
>
> The Tm of a DNA duplex increases by 1-1.5°C with every 1% decrease in homology. Thus, targets with greater than about 75% sequence identity would be observed using a hybridization temperature of 42°C. Such a sequence would be considered substantially homologous to the nucleic acid sequence of the present invention.

The applicants obtained three strains (C42, I73, H31) using an insect entrapment method. I73 and H31 belong to the species X. bovienii. All three species were determined to have an effective nematocide. I73 was cloned and DNA sequence analysis was performed on the clone. The final sequence of the clone is shown in Figure 2 (37,544 bps) and the corresponding protein sequences are present in Annex 1 (Annex 1 has 51 amino acid sequences). The applicants identified that two regions of the clone were involved in nematocidial activity, p13-1f (SEQ ID NO: 22) and p14-2f (SEQ ID NO: 23). The as-filed specification provides sufficient description of a species of an isolated nucleic sequence encoding SEQ ID NO: 23. However, there is no evidence of record that p14-2f had a known structural relationship to a genus of nematode control agent DNA sequences. Based upon the prior art and the difference between the nucleotide sequence of SEQ ID NO: 23 and SEQ ID NO: 22 there is expected to be variation among species of DNA sequences that encode nematode control agents. The specification does

not describe which nucleotide(s) of the sequence that encodes SEQ ID NO: 23 or what amino acid(s) of SEQ ID NO: 23 are considered essential for the biological activity of a nematode control agent. In view of the above considerations one of skill in the art would not recognize that the specification sufficiently describes a genus of claimed nucleotide sequences because SEQ ID NO: 23 is not a representative species of the claimed genus of isolated nucleotide sequences. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of isolated nucleic acid sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of isolated nucleic acid sequences that must exhibit the disclosed biological functions as contemplated by the claims.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purpose of the 'written description' inquiry, *whatever is now claimed.*" The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

With the exception of the nucleic acid sequence encoding SEQ ID NO: 23, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or the simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers

v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that, "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with all it claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only the nucleotide sequence encoding SEQ ID NO: 23, but not the full breadth of the claims (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus of nucleotide sequences encoding a nematode control agent peptide is highly variant.

Applicant's arguments filed 1/31/05 have been fully considered but they are not persuasive.

Applicant argues that in view of Example 9 in The Synopsis of Written Description Guidelines published by the USPTO the present claims meet written description requirement and because of the addition of the limitation of hybridization conditions in the instant claims.

Applicant arguments with respect to Example 9 are not found persuasive because of the reasons set forth in the examiner's response to applicant's argument under 112 written description in the prior office action mailed on 7/27/04. In addition, Example 9 is directed to an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclases activity. The DNA molecule set forth in the claimed invention is not directed to a nucleic acid that encodes a protein that binds a receptor and stimulates a specific activity. Thus, Example 9 does not correlate to applicant's claimed invention.

Furthermore, the hybridization conditions for a nucleic acid comprising a portion of SEQ ID NO: 52, the portion encoding the amino acid set forth in SEQ ID NO: 23 as recited in the instant claims are not disclosed in the specification. The instant specification discloses

hybridization conditions for a probe of 200 bp and not for a portion of the nucleic acid set forth in SEQ ID NO: 52 encoding the amino acid sequence set forth in SEQ ID NO: 23. See page 16 of the instant specification. The prior art does not provide the guidance lacking from the instant specification for making the claimed genus of nucleic acids. Thus, the hybridization conditions are not for the claimed nucleic acid molecules and the claimed genus of nucleic acid molecules is not supported by the specification.

In addition, while it is acknowledged that the skilled artisan can align two nucleic acid sequences with specific % identity using a hybridization method, one skilled in the art cannot determine from the hybridization method if the nucleic acid encodes a protein having nematode toxic activity indicating that the applicant did not have possession of the claimed genus of nucleic acid molecules at the time the application was filed.

The Statutory Declaration of James Morgan filed 1/31/05 is moot for overcoming the rejection of claims 43, 45-48, and 53 based upon 112 first paragraph written description rejection as set forth in the last Office action because the rejection was removed in view of the cancellation of the claims and Dr. Morgan does not address the new 112 first paragraph written description rejection.

Claims 57-64 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleotide sequence encoding the polypeptide set forth in SEQ ID NO: 23, does not reasonably provide enablement for an isolated nucleotide sequence encoding a polypeptide with up to 98% identity to SEQ ID NO: 23. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The invention lies in the field of producing a genus of isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and using the isolated nucleic acid molecule for generating a toxic response in a nematode.

The as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use a genus of isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode other than the sequence itself. The claims embrace a genus of isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode. The instant specification fails to provide guidance as to which (if any) of the amino acids may be changed while activity is retained. There are 1,673 amino acids in the polypeptide sequence set forth in SEQ ID NO: 23. The total number of 1,673 amino acid peptides is 4×10^{2176}. The number of single amino acid substitutions is 33,460. The

number of two amino acid substitutions is over $5x10^8$. The teaching in the specification do not commensurate in scope with the claims because the breadth of the claims embrace a large number of possible sequences that differ from SEQ ID NO: 23 by substitution of up to 30% of its amino acids, which would be a substitution of up to 501 amino acids of SEQ ID NO: 23. To determine the number of possible amino acid sequences, N, with 501 substitutions, one skilled in the art would use the formula [$(N=x^nL!/n!(L-n)!$), where x=19 (number of possible amino acids that could replace an amino acid at any one position in SEQ ID NO: 23), L=1673 (amino acid length of SEQ ID NO: 23), n=501,] or $3x10^{1082}$ possible sequences. This is a lower limit of the number of possible sequences because the claims also embrace insertions or deletions of amino acids in SEQ ID NO: 23 that the equation does not take into account. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The instant specification does not provide sufficient guidance and/or factual evidence that it was routine to substitute or delete at least two nucleotides of a nucleotide sequence and determine which nucleotide sequences meet the functional limitation of the claims. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Baker et al., Science, 294:pages 93-96, 2001); Attwood, T (*Science*, vol. 290, no. 5491, pp. 471-473, 2000); Gerhold et al., (*BioEssays*, vol. 18, no. 12, pp. 973-981, 1996); Russell et al.,

Journal of Molecular Biology, vol. 244, pp 332-350, 1994); and Wells et al., *Journal of Leukocyte Biology*, vol. 61, no. 5, pp. 545-550, 1997). Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain activity, and the fact that the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have at least 70% sequence identity to a polypeptide encoded by SEQ ID NO: 23 and wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and still possess nematocidial activity. Since it would require undue experimentation to identify other polypeptides that have nematocidial activity, it certainly would require undue experimentation to make their corresponding DNA, and therefore, the entire scope of the claimed invention.

In conclusion, the as-filed specification and claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or evidence to reasonably enable making and using an isolated nucleotide sequence encoding the polypeptide set forth in SEQ ID NO: 23, does not reasonably provide enablement for a genus of an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode. One

skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing a genus of isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode.

Applicant's arguments filed 1/31/05 have been fully considered but they are not persuasive.

Applicant argues that in view of recitation of quite stringent hybridization conditions in the claims, one skilled in the art could make and use the nucleic acids without undue experimentation. The specification teaches straight forward assays for determining whether a nucleic acid molecule encodes a polypeptide toxic to a nematode (pages 31-37 of the specification). Those skilled in the art are aware of various random mutagenesis protocols can be used to create libraries of clones encoding variant polypeptides. Although it cannot always be predicted whether a given amino acid change will alter function, it is generally understood, despite some exceptions, that certain types of variants, e.g., those involving conservative amino acid substitutions are **more likely** to retain function.

Applicant's argument directed to the recitation of quite stringent hybridization conditions is not found persuasive because while it is acknowledged that the skilled artisan can align two nucleic acid sequences with specific % identity using a hybridization method, one skilled in the art cannot reasonably extrapolate from the hybridization method to determining if the nucleic

acid encodes a protein having nematode toxic activity without an undue amount of experimentation.

Applicant's assertion that the conditions recited in the claims is quite stringent is not found persuasive because applicants do not provide any guidance and/or evidence to support that the conditions recited in the claims are quite stringent. In addition, the conditions recited in the claims are directed to an average probe of 200 bases as taught in the specification and not for the nucleic acid set forth in the instant claims.

With respect to applicant's argument directed to the specification teaches assays for determining whether a nucleic acid encodes a polypeptide that is toxic to a nematode, the argument is not found persuasive because the instant claims are directed to a product and not a method of determining whether or not a nucleic acid encodes a polypeptide that is toxic to a nematode.

With respect to applicant's argument that those skilled in the art are aware of various random mutagenesis protocols for producing a library of clones encoding variant polypeptides, the argument is not found persuasive because the applicant does not cite any protocols that were available at the time the invention was made for producing a genus of an isolated nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide having an amino acid sequence that is at least 70% identical to SEQ ID NO: 23, wherein the isolated nucleic acid molecules hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at 57°C in 0.368 M Na+ and 50% formamide and wherein the polypeptide is toxic to nematode. More specifically, the prior art is absent for producing at least $3x10^{1082}$ sequences and screening each sequence to determine whether or not the sequence encodes a polypeptide that is toxic to

nematodes. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 693-696, Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In addition, the claims are directed to a product not a method of producing a library of clones using random mutagenesis protocol.

With respect to applicant's argument that it is generally understood, despite some exceptions, that certain types of variants, e.g., those involving conservative amino acid substitutions are **more likely** to retain function, the argument is not found persuasive because the claims are broader than a nucleic acid encoding conservative amino acids.

The Statutory Declaration by James Morgan filed 1/31/05 is insufficient to overcome the rejection of new claims 57-64 and 66-70 based upon 112 first paragraph enablement because given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have need to have conducted undue and excessive experimentation in order to practice the claimed invention. This is further supported by Dr. Morgan statement "In this way rough experimental conditions can be established where segments of DNA with very similar and very different DNA sequences can be isolated" because one skilled in the art would have to perform

trial and error experimentation on DNA sequences that meet the first limitation of the claims to determine if the DNA sequences also have the claimed activity (toxic to nematode). See MPEP 2164.05(a), which recites that the specification must be enabling of the filing date. Thus, if the guidance in the specification requires one skilled in the art to perform trial and error experimentation on each DNA sequences to determine which sequences meets the functional limitation of the claims, this would indicate that the specification was not enabling as of the filing date.

Dr. Morgan states that in view of the DNA hybridization methods in the patent application and common textbooks, genes with very different sequences can be isolated using DNA hybridization as a key tool. See Winstanley 1994, Microbiology, 140:2019. The statement by Dr. Morgan is insufficient to overcome the enablement rejection because the instant claims are directed to a product and not a method of using DNA hybridization to isolated genes with very different sequences. In addition, while it is acknowledged that the skilled artisan can align two nucleic acid sequences with specific % identity using a hybridization method, one skilled in the art cannot reasonably extrapolate from the hybridization method to determining if the nucleic acid encodes a protein having nematode toxic activity without an undue amount of experimentation. Winstanley (supra) does not support practicing the claimed invention because the article is directed to a method of obtaining flagellin genes from two *Psuedomonas* strains and not the claimed products. The article does not use the material and methods that are recited in the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 is vague and indefinite because of the phrase "claim 53 for claim 57" on line 2 of claim 67. It is not apparent if the term is directed to two claims (claim 53 or claim 57) or is the claim incorrectly drafted and supposed to refer to using the vector of claim 53 in a method claim.

The rejection would be moot, if applicant amended the phrase to recite: -- claim 53 or claim 57 --.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The isolated nucleic acid molecule in instant claim 56 reads on a portion of the nucleotide sequence of SEQ ID NO: 52, wherein the portion comprises a nucleotide sequence encoding a polypeptide of any size from the amino acid sequence of SEQ ID NO: 22 and 23.

Claim 56 is rejected under 35 U.S.C. 102(b) as being anticipated by Thiele et al (Eur. J. Epidemol. 10:413-420, 1995). Thiele teaches a plasmid comprising a nucleotide sequence

comprising a portion of the nucleotide sequence that encodes a polypeptide with 6 amino acids of SEQ ID NO: 23 (amino acids 1105-1111). See amino acids 582-588 of the amino acid sequence taught by Thiele. In addition, the plasmid comprises a nucleotide comprising a portion of the nucleotide that encodes a polypeptide with two amino acids of SEQ ID NO: 22 (101-102). See amino acids 690-691 of the amino acid sequence taught by Thiele.

The search result displaying SEQ ID NO: 23 against the amino acid sequence encoded by the plasmid taught by Thiele is attached to the journal article.

Conclusion

Claims 53-55 and 65 are free of the prior art of record.

The isolated nucleic acid molecule in instant claims 57-64 reads on a nucleotide sequence encoding a polypeptide having an amino acid sequence of any length that has a portion that is at least 70% identical to SEQ ID NO: 23 wherein the isolated nucleic hybridizes to the portion of SEQ ID NO: 52 encoding SEQ ID NO: 23 at a particular set of hybridization conditions and wherein the polypeptide is toxic to nematodes. However, the claims are not rejected over the prior art because the prior art only teaches the structural limitation of the instant claims and not the functional limitation (toxic to nematodes).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Brian Whiteman
Patent Examiner, Group 1635

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